DETAILED ACTION

Status of Claims

1. Applicants' preliminary amendments, filed 7/20/2007, canceling Claims 2, 3, 8-10, 12, 13, 18-41 and 47-52 and amending the Specification, are acknowledged.

2. Applicants' Information Disclosure Statements, filed 3/16/2005 and 6/14/2007, are acknowledged and have been reviewed.

3. Applicants' election without traverse of Claims 1 and 4-7 (Group I, drawn to a method of treating or preventing stress response comprising administering a CCR5 antagonist) in the reply filed on 3/28/2008 is acknowledged. The Restriction Requirement is thus deemed to be proper and is made Final.

4. Applicants' election without traverse of the CCR5 antagonist species Compound A, as disclosed on page 28 of the instant Specification, is acknowledged. The Election of Species Requirement is thus deemed to be proper and is made Final.

5. Upon further consideration, the requirement to elect a subject species is withdrawn.

6. Claims 1, 4-7, 11, 14-17 and 42-46 are pending.

7. Claims 11, 14-17 and 42-46 are withdrawn from consideration in accordance with 37 CFR 1.142(b), because they are contained in non-elected groups.

8. Claims 1 and 4-7 are presently under consideration.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter, which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the Specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). (As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”)

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, the breadth of the claims, state and predictability of the art, and relative skill of those in the art

The invention relates to methods of treating or **preventing** "stress response" in a subject in need thereof, comprising administering a therapeutically effective amount of a CCR5 antagonist.

The diseases and conditions which read on the instant claims are extensive and open-ended. The definition of "stress response" (the condition treatable by the instant methods) provided by the instant Specification is "any response (i.e., physiological change) seen in a subject exposed to an insult (which may alternatively be referred to as a stressor)". The Specification defines an insult as "a trauma…or a physiopathological state…that results in changes to existing rhythmical processes which are homeostatic in nature". The stress response will vary, depending upon the type of

trauma and the physiological state of the subject. Disease conditions would include cancer, HIV and other viral and bacterial infections, transplant rejection, and bone fractures. It is unlikely that all diseases and conditions which read on "stress response" would be preventable by a CCR5 antagonist. For instance, at the present time, those skilled in the art would not accept that AIDS from HIV infection is preventable, although it can be effectively treated.

The prior art teaches the use of the instantly elected compound for the treatment of certain inflammatory and immunological conditions and disease. See Finke et al. (WO 00/76972 A1), discussed in the 35 USC 102 rejection, below.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicants' invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ 2d 1702 (Appellant's invention concerns

pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, 1st Paragraph is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). To that extent, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp v. Genetech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

Merriam-Webster's Online Dictionary defines the term "prevent" as "to keep from happening or existing, to deprive of power or hope of acting or succeeding ". The interpretation of the instant claims allows for the complete cure and eradication or total elimination of “stress response” by the administration of any CCR5 receptor antagonist.

In the present case, the claims recite methods of use comprising the administration of a plethora CCR5 receptor antagonist compounds. Whether any

particular compounds encompassed by the claims would have activity *in vivo*, would require synthesis and purification of the compound followed by testing. Predicting, *a priori*, whether a given compound would prevent any of the conditions as instantly claimed does not appear to be possible, especially since it is unlikely that all "stress response" has a CCR5-related etiology. Furthermore, the skilled artisan would not accept the suggestion that any one compound could be effective in preventing all "stress response" related diseases and conditions.

2. The amount of direction or guidance provided and the presence or absence of working examples

Applicants provide two *in vivo* working examples utilizing Compound A. "EXAMPLE 1" (pages 46-50) alleges fever suppression after cardiac allotransplantation. "EXAMPLE 3" (pages 51-52) alleges a decrease of plasma IL6 levels in the cardiac allotransplantation subjects (cynomologous monkeys) of EXAMPLE 1. Applicants suggest the data indicate "that the administration of a CCR5 antagonist such as Compound A can substantially reduce or suppress IL6 levels associated with an inflammatory response". Applicants provide an *in vitro* working example ("EXAMPLE 4, page 53) of the effect of Compound A on cytokine expression in cultured human macrophages.

It is noted that the only *in vivo* examples disclosed by Applicants are drawn to graft transplant subjects. No examples are provided demonstrating prevention.

Guidance is provided only for treatment of symptoms related stress induced increases of the pro-inflammatory cytokines, IL1 and IL6 (i.e., administration of CCR5

receptor antagonists are alleged to reduce IL1 and IL6 levels). However, inhibition of a receptor does not necessarily correlate to clinical efficacy. Additionally, the body's reaction to stressors involves effects on many other hormonal and neurogenic pathways (e.g., adrenaline, ACTH, endorphin release, activation/inhibition of sympathetic and parasympathetic pathways, etc.)

Doses required to practice their invention are described at page 45 of the Specification. A 1,000,000-fold range of doses is disclosed (e.g., 0.001 to 1000 mg/kg/day), which may be administered in single or multiple doses.

3. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that all CCR5 antagonist compounds could be predictably used to prevent all maladies involving a "stress response" to a trauma, as inferred in the claims and contemplated by the Specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because CCR5 receptor antagonists can inhibit pro-inflammatory cytokines IL1 and IL6 and that inflammation is a condition that may be associated with the body's "stress response" to

some trauma, they must therefore, *a priori*, be useful in the prevention of any "stress response" related disease or condition. The claims can encompass a multitude of chemically and biologically distinct compounds. Applicants present evidence for a single CCR5 antagonist, Compound A. Determining if any particular disclosed compound would prevent all "stress response" related diseases and conditions would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy. Further, as discussed *supra*, while pro-inflammatory cytokines have been implicated in some diseases, simply inhibiting these cytokines (IL1 and IL6) does not predictably correlate to clinical prevention of these diseases.

Some CCR5 receptor antagonist compounds have been shown to be useful as therapeutic agents for the <u>treatment</u> of various "stress responses". However, the claims encompass the utilization of the claimed compounds in the *prevention* of the recited diseases. As discussed *supra*, to prevent is to stop from occurring and, thus, requires a higher standard for enablement than does "treat". It is well accepted in the medical art that a majority of diseases cannot be totally prevented with current therapies. In addition, the present Specification lacks guidance and/or working examples of the utilization of the claimed compounds in the prevention any of the recited diseases and,

thus, does not enable those skilled in the art to which it pertains to use the invention commensurate in scope with these claims.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person skill in the art would have to engage in undue experimentation, with no assurance of success.

11. Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the Specification, while being enabling for treating conditions such as fever suppression and decreased abdominal tenderness following cardiac allotransplantation, does not reasonably provide enablement for treating any “stress response” of any etiology. The Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the Specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). (As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”)

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC

1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833,839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, the breadth of the claims, state and predictability of the art, and relative skill of those in the art</u>

The invention relates to methods of treating or preventing "stress response" in a subject in need thereof, comprising administering a therapeutically effective amount of a CCR5 antagonist. The instant Specification discloses compounds of Formulae (I) and (II) as suitable for use in the methods of the instant invention in addition to compounds having CCR5 antagonist activity that are not defined by the formulae.. Since no specific

CCR5 antagonists are recited by the instant claims, the broadest interpretation of the claims in light of the Specification would read on all compounds defined by Formulae (I) and (II), as well as all other compounds that have CCR5 antagonist activity.

Likewise, the diseases and conditions which read on the instant claims are extensive and open-ended. The definition of "stress response" (the condition treatable by the instant methods) provided by the instant Specification is "any response (i.e., physiological change) seen in a subject exposed to an insult (which may alternatively be referred to as a stressor)". The Specification defines an insult as "a trauma…or a physiopathological state…that results in changes to existing rhythmical processes which are homeostatic in nature". The stress response will vary, depending upon the type of trauma and the physiological state of the subject. It is unlikely that all diseases and conditions which read on these definitions would be treatable by any one compound.

The prior art teaches the use of the instantly elected compound for the treatment of certain inflammatory and immunological conditions and disease (*supra*).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicants' invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the

scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ 2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112, 1st Paragraph is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). To that extent, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp v. Genetech, Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

The skilled artisan would not likely accept the suggestion that CCR5 antagonists could be effective in treating all "stress response" related diseases and conditions, especially since it is unlikely that all "stress response" has a CCR5-related etiology.

2. The amount of direction or guidance provided and the presence or absence of working examples

Applicants provide two *in vivo* working examples. "EXAMPLE 1" (pages 46-50) alleges fever suppression after cardiac allotransplantation. "EXAMPLE 3" (pages 51-52) alleges a decrease of plasma IL6 levels in the cardiac allotransplantation subjects (cynomologous monkeys) of EXAMPLE 1. Applicants suggest the data indicate "that the administration of a CCR5 antagonist such as Compound A can substantially reduce or suppress IL6 levels associated with an inflammatory response". Applicants provide an *in vitro* working example ("EXAMPLE 4, page 53) of the effect of Compound A on cytokine expression in cultured human macrophages.

It is noted that the only *in vivo* examples disclosed by Applicants are drawn to graft transplant subjects.

Guidance is provided only for treatment of symptoms related stress induced increases of the pro-inflammatory cytokines, IL1 and IL6 (i.e., administration of CCR5 receptor antagonists are alleged to reduce IL1 and IL6 levels). However, inhibition of a receptor does not predictably correlate to clinical efficacy. Additionally, the body's reaction to stressors involves effects on many other hormonal and neurogenic pathways (e.g., adrenaline, ACTH, endorphin release, activation/inhibition of sympathetic and parasympathetic pathways, etc.)

Doses required to practice their invention are described at page 45 of the Specification. A 1,000,000-fold range of doses is disclosed (e.g., 0.001 to 1000 mg/kg/day), which may be administered in single or multiple doses.

3. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds defined by Formulae (I) and (II) would all be effective as CCR5 antagonist or that these compounds and other, undisclosed CCR5 antagonist compounds could be predictably used as a treatment for all maladies involving a “stress response” to a trauma, as inferred in the claims and contemplated by the Specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because CCR5 receptor antagonists can inhibit pro-inflammatory cytokines IL1 and IL6 and that inflammation is a condition that may be associated with the body's "stress response" to some trauma, they must therefore, *a priori*, be useful in the treatment of any “stress response” related disease or condition. However, the claims can encompass a multitude of chemically and biologically compounds. Applicants appear to have

synthesized a small number of compounds and tested them for antagonism of the CCR5 receptor. Determining if any particular disclosed compound would treat all "stress response" related diseases and conditions would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy. Further, as discussed *supra*, while pro-inflammatory cytokines have been implicated in some diseases, simply inhibiting these cytokines (IL1 and IL6) does not predictably correlate to clinical treatment of these diseases.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person skill in the art would have to engage in undue experimentation, with no assurance of success.

12. Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of treating or preventing stress response in a subject in need thereof, comprising administration of a therapeutically effective amound of a CCR5 antagonist. No specific CCR5 antagonist is claimed.

In the present case, the claims recite methods of use comprising the administration of a plethora of chemically distinct compounds, defined by the structure of instant Formulae (I) and (II), and other compounds not defined by the formulae (and not recited in the Specification) which have CCR5 antagonist activity. The substituents of the disclosed formulae, designated as R1 to R8, encompass a multitude (thousands, if not millions) of possible chemical structures. Whether any particular compounds encompassed by the formulae would have any CCR5 receptor antagonist activity *in vitro*, let alone *in vivo*, would require synthesis and purification of the compound followed by testing in an *in vitro* or *in vivo* assay. Predicting, *a priori*, whether a given compound is an antagonist of the CCR5 receptor in a cell or treat any of the conditions as instantly claimed does not appear to be possible.

Applicants disclose one specific compound which read on the invention and disclose by incorporation of other patents and patent applications, a relative handful of compounds that allegedly read on the instant disclosure. As such, it is not apparent that Applicants were actually in possession of, and intended to use, within the context of the present invention, all compounds for Formulae I and II, and all known CCR5 antagonists, at the time the present invention was made.

Claim Rejections - 35 USC § 102

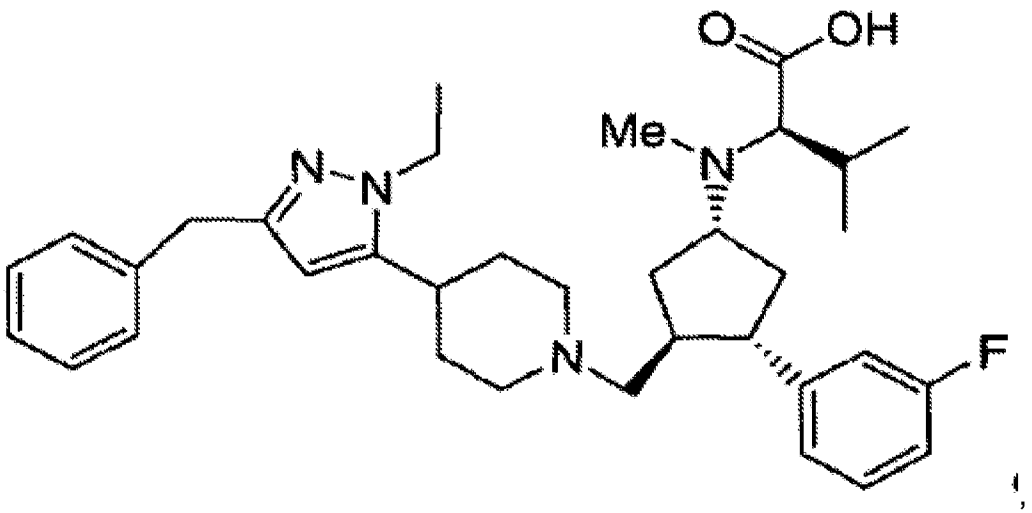
13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 1, 4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Finke et al. (WO 00/76972 A1, *see* Applicants' IDS filled 3/16/05).

Finke et al. teach *inter alia* compounds useful as antagonists of chemokine receptor CCR5. See page 55, lines 16-29. Finke et al. teach the compound:



which is the instantly elected CCR5 antagonist (compound A, disclosed on page 28 of the instant Specification). Finke et al. teach CCR5 antagonists are useful in the treatment of *inter alia* diseases and conditions associated with inflammation and infection, including graft rejection, reperfusion injury, atherosclerosis, septic shock and HIV infection. See line 10, page 53 through line 2, page 54; and page 55, 2nd paragraph. Treatment of these diseases and conditions all read on the instant claim of treating "stress response". See the instant Specification definition of "stress response" on page 6, last paragraph. Since the above recited compound of Finke et al. is identical to the instantly elected compound, it will also inhibit "endogenous production of one or more pro-inflammatory cytokines selected from the group consisting of IL1 and IL6" as

recited by instant Claim 7, absent evidence to the contrary. It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Also see *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finke et al. (WO 00/76972 A1).

The teachings of Finke et al. are presented *supra*.

As presented *supra* Finke et al. teach CCR5 antagonists are useful in the treatment of diseases and conditions associated with *inter alia* inflammation and infection, including graft rejection, and reperfusion injury. These are all conditions which might occur as a result of surgery, and in particular, cardiac surgery. It would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the CCR5 antagonist compounds taught by Finke et al. to treat (or pre-treat) these stress

response related reactions of surgical patients, including those patients undergoing cardiac surgery. Said artisan would have been motivated to reduce the inflammation, fever, malaise and potential for infection which often accompany surgery. Reperfusion injury and graft reject are potential responses to cardiac surgery. Amelioration of these conditions eases patient discomfort and hastens patient prognosis and recovery.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

18. Claims 1 and 4-7 are rejected.

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1611

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614